Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1, 27, 28, and 37 have been amended, and new claims 67 and 68 have been added. Descriptive support for the claim 1 amendments is found on page 4, lines 9-13; page 19, line 17 to page 20, line 20; and at Tables 2 and 3. Descriptive support for the claim 37 amendments is provided in original claim 43. New claims 67 and 68 are supported by the results presented in Tables 2 and 3. No new matter has been added by way of the above amendments.

Claims 26, 38-41, 43, and 62-66 have been cancelled without prejudice.

Claims 1-25, 27-37, 42, 44-61, 67, and 68 are pending, with claims 29-36 and 44-61 standing withdrawn. No excess claim fees are due with this submission.

The rejection of claims 1-3, 5, 6, 9, 10, 14, 15, 17-24, 37, 39, 41, and 42 under 35 U.S.C. § 102(b) as being anticipated by Dubertret et al., "Single-mismatch Detection using Gold-quenched Fluorescent Oligonucleotides," *Nature Biotech.* 19:365-370 (2001) ("Dubertret") is respectfully traversed.

Dubertret teaches the detection of single-mismatch by using gold nanoparticles covalently linked to hairpin nucleic acid probes tagged with a fluorophore. However, Dubertret fails to teach or suggest each and every limitation of the claimed subject matter. Dubertret fails to teach or suggest both the presence of "plurality of spacer molecules bound to the fluorescence quenching surface" and the binding of such spacer molecules "following exposure of the fluorescence quenching surface to a mixture comprising a ratio of spacer molecule to first nucleic acid molecule of about 5:1 or greater" as recited in claim 1.

The rejection of claims 37, 39, 41, and 42 is overcome by the amendment of claim 37 to recite the Markush group of original claim 43.

For these reasons, the rejection of claims 1-3, 5, 6, 9, 10, 14, 15, 17-24, 37, 39, 41, and 42 for anticipation by Dubertret is improper and should be withdrawn.

The rejection of claims 1-11, 14-21, 24, 26-28, and 37-42 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,312,906 to Cass et al. ("Cass") is respectfully traversed.

Cass generally teaches the use of surface bound hairpin nucleic acids for detection of target nucleic acids. While Cass describes the use of dithiols to control hairpin

density, Cass provides no guidance for their use and none of the Examples illustrate their use. Thus, Cass fails to teach or suggest the binding of disclosed dithiols and nucleic acid molecules "following exposure of the fluorescence quenching surface to a mixture comprising a ratio of spacer molecule to first nucleic acid molecule of about 5:1 or greater" as recited in claim 1. Moreover, none of the examples provided by Cass demonstrate "at least a 5-fold increase in fluorescent emissions intensity when the sensor chip is exposed to a target nucleic acid molecule that hybridizes specifically to the first nucleic acid molecule." Examples 1-3 of Cass are prospective, do not describe using a spacer molecule, and report no results. The chip described in Example 4 yielded a less than 2-fold increase, and the chip described in Example 5 yielded a 2-fold increase. Example 6 describes chip formation in the absence of any spacer molecules without reporting any results. The chip described in Example 7 yielded a nearly 3-fold increase, the chip described in Example 8 yielded a 3-fold increase, and the chip described in Example 9 yielded a less than 2-fold increase. Cass, therefore, fails to teach or suggest the critical need for the recited ratio of spacer to nucleic acid molecule with respect to the recited fold-increase in fluorescence.

With regard to claim 21, Cass teaches away from the claimed subject matter. Cass recites that only a single species of nucleic acid probe is used at each discrete and isolated region on an array (col. 12, lines 8-10; and col. 13, line 65 to col. 14, line 2). Because Cass teaches exactly the opposite of what is claimed, Cass cannot anticipate the recited subject matter, and Cass certainly would not have rendered it obvious.

The rejection of claim 37-42 is overcome by the amendment of claim 37 to recite the Markush group of nucleic acid probes of original claim 43.

For these reasons, the rejection of claims1-11, 14-21, 24, 26-28, and 37-42 as anticipated by Cass is improper and should be withdrawn.

The rejection of claims 12, 13, 22, and 23 for obviousness under 35 U.S.C. § 103(a) over Cass in view of U.S. Patent Publ. No. 2002/0034747 to Bruchez et al. ("Bruchez") is respectfully traversed.

Bruchez is cited at page 7 of the office action for teaching use of semiconductor nanocrystal labels attached to different polynucleotides for simultaneous analysis. Because the PTO has failed to demonstrate how Bruchez overcomes the noted deficiencies of Cass, the rejection of claims 12, 13, 22, and 23 for obviousness over the combination of Cass and Bruchez is improper and should be withdrawn.

The rejection of claims 25 and 43 for obviousness under 35 U.S.C. § 103(a) over Cass in view of Vannuffel et al., "Specific Detection of Methicillin-Resistant *Staphylococcus* Species by Multiplex PCR," *J. Clin. Microbiology* 33(11):2864-2867 (1995) ("Vannuffel"), Berger-Baechi et al., Genbank accession No. X17688 ("Berger-Baechi") and U.S. Patent No. 5,541,308 to Hogan et al. ("Hogan") is respectfully traversed.

The teachings and deficiencies of Cass with respect to claim 1 are noted above. Vannuffel teaches detection of *femA* gene of methicillin-resistant Staphylococcus species by using two different oligonucleotide probes that detect and are complementary to PCR-amplified regions of *femA*. Berger-Baechi teaches the entire sequence of the *femA* gene. Hogan teaches method of preparing oligonucleotides that are sufficiently complementary to a unique region of rRNA for a hybridization assay. The PTO asserts at page that it would have been obvious to a person of ordinary skill in the art to use the *femA* sequence taught by Berger-Baechi and Vannuffel to design *femA*-specific probes as taught by Hogan and use such probes in a manner taught by Cass. Applicants respectfully disagree.

With respect to claim 25, none of the secondary references, alone or in combination, overcomes the above-identified deficiencies of Cass in relation to claim 1 (upon which claim 25 depends). Therefore, the rejection of claim 25 is improper and should be withdrawn.

With respect to claim 43 (now presented in claim 37), none of the references teaches or suggests the specific probes recited. Based on the sequence of *femA* reported in Berger-Baechi, thousands of different probes could be formed. Vannuffel only identifies two of them. However, the issue is not just whether the person of skill in the art could have identified any of the specific probes that are presently claimed but rather whether the combined teachings of these references would have taught or suggested to the person of ordinary skill in the art these specific probes. Given the thousands of possibilities, applicants submit that mere knowledge of the whole *femA* sequence and general methods of probe design is insufficient to demonstrate the obviousness of the claimed probes. Accordingly, the rejection of claim 43 is improper and should be withdrawn.

The provisional rejection of claims 1-28 and 37-43 on the basis of nonstatutory obviousness-type double patenting over claims 1-14 of copending U.S. Patent Application Serial No. 11/838,616 to Miller et al. ("Miller I") is respectfully traversed.

Miller I relates to a hairpin probe (and sensor) that can detect methicillin-resistant *Staphylococcus* spp. The claimed probes of Miller I are characterized by

hybridizing "over substantially the entire length thereof to nucleic acids of methicillin resistant *Staphylococcus* spp."

Claim 37 now recites specific probes, including SEQ ID NOS. 1 and 2, but neither of these hybridizes over substantially their entire length to nucleic acids of methicillin resistant *Staphylococcus* spp. That is because the stems of these hairpins do not hybridize with the target nucleic acid. While a number of other specifically recited probes hybridize over their full length to a target nucleic acid molecule (SEQ ID NOS: 3-10), the target is not from methicillin resistant *Staphylococcus* spp. Thus, the claimed probes of claim 37 would not have been obvious over claim 1 of Miller I.

Claim 1 as amended recites the presence of a "plurality of spacer molecules bound to the fluorescence quenching surface" and that the spacer molecules and nucleic acid molecule "are bound to the fluorescence quenching surface following exposure of the fluorescence quenching surface to a mixture comprising a ratio of spacer molecules to first nucleic acid molecules of about 5:1 or greater." Moreover the sensor chip of claim 1 exhibits at least a 5-fold increase in fluorescence emission intensity when exposed to a target nucleic acid. These limitations are neither taught nor suggested by the claims of Miller I.

For these reasons, the provisional obviousness-type double patenting rejection of claims 1-28 and 37-43 over claims of Miller I is improper.

The provisional rejection of claims 1-28 and 37-43 on the basis of non-statutory obviousness-type double patenting over claims 18-26 of U.S. Patent Application Serial No. 10/584,875 to Miller et al. ("Miller II") is moot because claims 18-26 of Miller II were cancelled in an amendment filed in October 2006.

The provisional rejection of claims 1-28 and 37-43 on the basis of non-statutory obviousness-type double patenting over claims 1-8, 11, 13-14, and 17-21 of U.S. Patent No. 7,442,510 to Miller et al. ("Miller III") in view of Cass is respectfully traversed.

Miller III relates to hairpin probes and DNA molecules that hybridize over their full length to a target nucleic acid having a naturally occurring nucleotide sequence. The probes also include a label tethered to one terminus of the probe and a quenching agent tethered to the other terminus.

Claim 37 now recites specific probes, whereas the claims of Miller III do not recite any specific probes by sequence. Thus, the claimed probes would not have been obvious over any claims of Miller III.

Claim 1 as amended recites the presence of a "plurality of spacer molecules bound to the fluorescence quenching surface" and that the spacer molecules and nucleic acid molecule "are bound to the fluorescence quenching surface following exposure of the fluorescence quenching surface to a mixture comprising a ratio of spacer molecules to first nucleic acid molecules of about 5:1 or greater." Moreover the sensor chip of claim 1 exhibits at least a 5-fold increase in fluorescence emission intensity when exposed to a target nucleic acid. These limitations are not recited in any of the claims of Miller III, and Cass fails to overcome this deficiency for the reasons noted above.

Accordingly, this provisional rejection of claims 1-28 and 37-43 is improper and should be withdrawn.

Moreover, because the several provisional obviousness-type double patenting rejections are the only rejections that remain (i.e., all other rejections should be withdrawn for the reasons noted herein), these provisional rejections should be withdrawn pursuant to MPEP § 804 (*see* p. 800-17).

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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